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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/367,794	DIME ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Dispositi n of Claims

4)☒ Claim(s) *44,46,48-50,52,53,55-57,59-62 and 64-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44,46,48-50,52,53,55-57,59-62 and 64-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☒ Interview Summary (PTO-413) Paper No(s). *7/30/03* .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. The Request for Continued Examination (RCE) filed August 11, 2003 under 37 CFR 1.114 is acknowledged. An action on the RCE follows.

Status of the Claims

2. Claims 44, 46, 48-50, 52, 53, 55-57, 59-62 and 64-69 are pending.

Applicant's amendments filed on August 11, 2003 is acknowledged, and applicants' response has been fully considered. Claims 44, 46, 48, 52, 53, 55, 59, 62 and 64 have been amended, claims 45, 47, 51, 54, 58 and 63 have been cancelled, and new claims 67-69 have been added. Therefore, claims 44, 46, 48-50, 52, 53, 55-57, 59-62 and 64-69 are examined.

Objection Withdrawn

3. The previous objection to the drawings of Fig. 5A-5D and Fig. 8 is withdrawn in view of the clean copies of the drawings being submitted August 11, 2003, and Fig. 5A-5D and Fig. 8 have been entered.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

4. The previous rejection of claims 44-58 and 63 under 35 USC § 112, second paragraph, is withdrawn in view of applicants' amendment to the claim, applicants' cancellation of the claims, and applicants' response at pages 12-13 in the amendment filed August 11, 2003.

Claim Rejections - 35 USC § 102 and 102/103(a)

5. The previous rejection of claims 44, 47 and 51 under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as being obvious over Greenfield *et al.* (EP 0398305), is withdrawn in view of applicants' amendment to the claim, applicants'

cancellation of the claims, and applicants' response at pages 13-14 in the amendment filed August 11, 2003.

6. The previous rejection of claims 44, 47, 49-52, 54 and 56-58 under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as being obvious over Pouletty *et al.* (WO 95/10302), is withdrawn in view of applicants' amendment to the claim, applicants' cancellation of the claims, and applicants' response at pages 14-15 in the amendment filed August 11, 2003.

7. The previous rejection of claims 59-62 under 35 U.S.C. 102(e) as being anticipated by Fesik *et al.* (U. S. Patent 5,989,827), is withdrawn in view of applicants' amendment to the claim and applicants' response at pages 15-16 in the amendment filed August 11, 2003.

Claim Objections

8. Claims 46, 48, 49, 50, 53, 55-57, 62, 64-66 are objected to because the claim contains recitation of non-elected inventions.

In response, applicants indicate claims 46, 53 and 62 have been amended to set forth a list of small organic molecule drugs; the specific selected proteins recited in claims 48, 55 and 64 share the common utility as therapeutic protein targets to which A-L-D binds and the proteins share a structural feature of being members of groups of homologous proteins; the anchoring moieties in claims 49-50, 56, 57, 65-66 share the common utilities as a moiety that binds to a binding site on a specific selected protein and share the common structural feature of having a chemical functional group that can react with a specific selected protein at a first binding site (page 11 of the response). The response has been fully considered, however, the argument is not found persuasive because the drugs (e.g., antineoplastic agent; thiazolidinone (class 514/369); or

pyrrolidine (class 546/276.4) versus benzocaine (class 514/535) as local anesthetic), the specific selected proteins (e.g., membrane transporter or membrane receptor versus sodium ion channel) and anchoring moieties (e.g., α-halo ketone as alkylating agent or anhydride as acylating agent versus methanethiosulfonyl as sulfhydryl reactive group) do not have the same utility, nor share a substantial structural feature, these compounds are not considered as a Markush group having the unity of invention, thus the non-elected members are patentably distinct inventions from the elected compound and are withdrawn form consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 44, 46, 48-50, 52, 53, 55-57, 59-62 and 64-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for targeting a drug to a specific selected protein or identifying a drug that binds to a specific selected protein by contacting the specific selected protein with a compound having a formula A-L-D, wherein A is an anchoring moiety which binds to the first binding site of the specific selected protein, L is a linking group, and D is a drug that binds to a second binding site of the specific selected protein, and the first and the second binding sites are distinct, and wherein the structure of A-L-D (e.g., the benzocaine and lidocaine compounds listed in Fig. 2) and the specific selected protein (e.g., the sodium ion channel) are defined, does not reasonably provide enablement for a method for targeting a drug to a specific selected protein or identifying a drug that binds to a specific selected protein by contacting the specific selected protein with a compound having a formula A-

L-D, or, a method for identifying a compound of A-L-D that binds to a specific selected protein by contacting the specific selected protein with a compound having a A-L and subsequently combining the selected protein with a drug (D) from a library of drugs, wherein A is an anchoring moiety which binds to the first binding site of the specific selected protein, L is a linking group, and D is a drug that binds to a second binding site of the specific selected protein, and the first and the second binding sites are distinct, and wherein the structure of A-L-D is not defined and the specific selected protein is an ion channel or a membrane receptor but not specified. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 44, 46, 48-50, 52, 53, 55-57, 59-62 and 64-69 are directed to a method for targeting a drug to a specific selected protein (claims 44, 46, 48-50 and 67-69) or identifying a drug that binds to a specific selected protein (claims 59-62 and 64-66) by contacting the specific selected protein with a compound having a formula A-L-D, or, a method for identifying a compound of A-L-D that binds to a specific selected protein (claims 52, 53 and 55-57) by contacting the specific selected protein with a compound having a A-L and subsequently combining the selected protein with a drug (D) from a library of drugs, wherein A is an anchoring moiety which binds to the first binding site of the specific selected protein, L is a linking group, and D is a drug that binds to a second binding site of the specific selected protein, and the first and the second binding sites are distinct, wherein the specific selected protein is an ion channel or a membrane receptor. The specification, however, only discloses cursory conclusions without data supporting the findings, which states that the present invention provides

compounds and methods which are useful for tissue or cell-specific delivery and localization of drugs, where the compounds are represented by A-L-D, where A is an anchoring moiety, L is a linking group, and D is a drug, and the anchoring moiety is a functional group capable of covalent attachment to a target site (page 3, lines 1-13). There are no indicia that the present application enables the full scope in view of the method of targeting a drug to a specific selected protein or identifying a drug that binds to a specific selected protein by contacting the specific selected protein with a compound having a formula A-L-D as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the anchoring moiety and the drug in compound A-L-D, and the effect of the A-L-D targeting at the specific selected protein, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

Examples 1-11 indicate compounds containing an anchoring moiety of a sulfhydryl reactive group linked through a hydrocarbon or ethylene glycol chain to a local anesthetic drug

(i.e., benzocaine or lidocaine), and Example 12 indicates these agents are site specific and the anchoring group was anchored in the channel pore and delivered the drug to the local anesthetic binding site. No other working examples indicate the use of A-L-D with various anchoring group and drugs targeting different proteins.

(3). The state of the prior art and relative skill of those in the art:

The prior art (references at pages 1-2 of the specification) indicates the ion channel proteins in various tissues have distinct amino acid sequences, yet the tertiary structure and functional properties are very similar, and the domains which confer the essential functional properties of ion channel properties are highly conserved, thus the drugs which modulate ion channel proteins are inherently incapable of being directed specifically to specific ion channel proteins in one tissue without affecting other tissues. Although the specific targeting drugs to a receptor site such as drugs linked to antibodies (immunoconjugates) have been used for targeted drug delivery, their use have limitation because many cellular sites cannot be targeted with immunoconjugates; and the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the anchoring of A-L-D to various targeting proteins, and the effects of these site specific agents to be considered enabling.

(4). Predictability or unpredictability of the art:

The claims encompass a method for targeting a drug to a specific selected protein or identifying a drug that binds to a specific selected protein by contacting the specific selected protein with a compound having A-L-D. However, the specification has not demonstrated the use of the compounds containing various anchoring groups and drugs in targeting at various

selected proteins, nor has shown the effect of these compounds. Therefore, the invention is highly unpredictable regarding the outcome of the claimed method.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method for targeting a drug to a specific selected protein or identifying a drug that binds to a specific selected protein by contacting the specific selected protein with a compound having a formula A-L-D, or, a method for identifying a compound of A-L-D that binds to a specific selected protein by contacting the specific selected protein with a compound having a A-L and subsequently combining the selected protein with a drug (D) from a library of drugs. The specification indicates the targeting agents are compounds of A-L-D which bind to ion channel proteins, e.g., agents containing an anchoring moiety of a sulfhydryl reactive group linked through a hydrocarbon or ethylene glycol chain to a local anesthetic drug (i.e., benzocaine or lidocaine), where benzocaine is prototypic for class 1b agent with very rapid kinetics for binding or unbinding to Na^+ channels which is not tissue specific, however, the anchors take advantage of unique cysteine which is present in the P-loop of cardiac Na^+ channels but not in Na^+ channels of other tissues (page 3, lines 24-31; Fig 2; Examples 1-11), and these agents are site specific and the anchoring groups have delivered the drug to the local anesthetic binding site (Example 12). Although the identification of potential anchoring group binding sites of the targeted protein have been described, e.g., various binding sequences of cardiac Na^+ and K^+ channel proteins, or cardiac and smooth muscle Ca+2 channel proteins have been indicated, the agents that bind these sequences have not been identified (pages 21-24); and simple anchors such as sulfhydryl-reactive groups, alkylating agents and acylating agents, which bind covalently

to a target site can be attached to a drug to form site specific therapeutic agents (page 11). However, the specification has not identified the compounds of A-L-D comprising various anchoring groups and drugs aside from compounds in Fig. 2, nor has demonstrated the effects of the compounds targeting at specific selected proteins. There are no working examples demonstrating the compounds of A-L-D comprising various anchoring groups such as alkylating agents or acylating agents can target at specific selected proteins. Since the specification fails to provide sufficient teaching on the identities and the effects of various A-L-D in targeting specific proteins, it is necessary to have additional guidance to carry out further experimentation to assess the effects of these A-L-D compounds.

(6). Nature of the Invention

The scope of the claims encompasses a method for targeting a drug to a specific selected protein or identifying a drug that binds to a specific selected protein by contacting the specific selected protein with a compound having A-L-D, but the specification has not identified various A-L-D compounds and their effect in targeting specific proteins. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed method associated with variants, the outcome is unpredictable regarding the effects of the compound, and the teachings in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of A-L-D in the claimed method.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 52, 53 and 55-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 48, 52, 53, 55-57 and 64 are indefinite because the claim recites a method for identifying a compound of formula: A-L-D, however, the compound "A-L-D" does not form in the process. The claim indicates the anchoring moiety (A) in a compound comprising A and L (linking group) is attached to the first binding site of the specific selected protein in step (b), and then the specific selected protein is combined with one drug from a library of drugs that forms covalent bond with the linking group and also binds to the second binding site of the specific selected protein in step (c). Thus, according to the method, the conjugate of the protein and A-L forms in step (b), and the conjugate of the protein and A-L-D forms in step (c), thus it is not clear how to identify a compound of formula: A-L-D, which does not form in the process. Claims 53 and 55-57 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

12. Claims 48, 55 and 64 recite the limitation "a membrane transporter" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

13. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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October 28, 2003

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